IN THE CLAIMS:

Please amend claims 1, 2, 5, and 14 to read as follows:

1. **(Amended)** A method for the early detection and/or quantification of CNS damage in an individual, said CNS damage being caused by benign primary brain tumors, malignant primary brain tumors, brain metastasis, hydrocephalus, subdural haematoma, and/or parasite derived cysts of the CNS; by invasion or metastasis of the CNS; by organisms; by anoxia or ischemia; by chemical agents; by physical agents; or by a combination of these mechanisms, said method comprising the step of determining the level of tau in said individual and comparing it to the level of tau in control healthy individuals.

2. **(Amended)** A method for the early in vitro detection and/or quantification of CNS damage in an individual, said CNS damage being caused by benign primary brain tumors, malignant primary brain tumors, brain metastasis, hydrocephalus, subdural haematoma, and/or parasite derived cysts of the CNS; by invasion or metastasis of the CNS; by organisms; by anoxia or ischemia; by chemical agents; by physical agents; or by a combination of these mechanisms, said method comprising the steps of:

   - obtaining a sample from said individual,
   - determining the level of tau in said sample and comparing it to the level of tau in control healthy individuals.

5. **(Twice Amended)** A method according to claims 1 or 2 in which the CNS damage is cause by a benign primary brain tumor, a malignant primary brain tumor, a brain metastasis, or a subdural haematoma.

14. **(Amended)** A kit for the early diagnosis of CNS damage in an individual, said CNS damage being caused by benign primary brain tumors, malignant primary brain tumors, brain metastasis, hydrocephalus, subdural haematoma, and/or parasite derived cysts of the CNS; by invasion of the CNS; by organisms; by anoxia or ischemia; by chemical agents; by physical agents; or by a combination of these mechanisms, comprising a tool for the detection of tau.

REMARKS

I. Status of the claims

Claims 1, 2, 5, and 14 are amended.

Claims 1-11 and 14-17 are currently pending.

II. Support and rationale for the amendment

Support for the amendment is found at page 6, lines 24-27 of the specification. The amendment is made solely for procedural reasons (*i.e.*, in support of an argument for Unity of Invention). Accordingly, the amendment is not made for reasons relating to the patentability of the claims and is not believed to narrow the scope of the claims. A complete copy of the pending claims, including marked up versions of the amended claims is attached hereto.

III. Specific response to Restriction

In issuing the instant restriction requirement, the Examiner has restricted to the claims to one of IV groups, namely:

Group I: claims 1-3 and 5-11 drawn to detection/quantification of CNS damage based on analysis of cerebrospinal fluid.

Group II: Claims 1, 2 and 4-11 drawn to detection/quantification of CNS damage based on analysis of cerebrospinal fluid.

Group III: Claims 14-16 drawn to a kit comprising a tool for the detection of tau wherein the kit comprises a monoclonal antibody, a secondary antibody, a marker, and appropriate buffer solutions.

Group IV: Claim 17 drawn t a method for screen or monitor the effect of compounds which prevent or treat CNS damage.

In support of the Restriction Requirement, the Examiner alleged that the instantly pending claims do not define a "special technical feature which constitute an contribution over the prior art. The Examiner specifically alleges that claims 1-3, 16, and 17 are anticipated by WO 94/13795. The restriction goes on to assert that:

> [t]his patent application discloses that the invention aims at providing a process (method) for the detection or diagnosis in vitro of brain disease involving tau protein. This patent application also discloses that Alzheimer's disease (AD), a form of CNS damage in an individual, is characterized neuropathologically by the presence of neuritic (senile) plaques (holes or space-occupying lesions) and neurofibrillary tangles (NFT). Therefore, claims 1, 2, 3, 16, and 17 lack a special technical feature and cannot share one with the other claims.

Applicant responds as follows.

Claims 1, 2, and 14 are now amended to replace the limitation "space-occupying lesions" with the limitations "*benign primary brain tumors, malignant primary brain tumors, brain metastasis, hydrocephalus, subdural haematoma, and/or parasite derived cysts.*"

This amendment, clarifies the fact that CNS damage resulting from Alzheimer's disease (AD) is not encompassed by the types of CNS damage listed in the pending claims. Since the cited art does not teach or discuss any type of CNS damage other than that caused by AD, it does not anticipate any of the current claims. Furthermore, WO 94/13795 does not teach or suggest a relationship between tau levels and the types of CNS damage recited in the currently pending claims and therefore does anticipate the pending claims.

Applicant notes that PCT Rule 13 recites, *inter alia*:

> Where a group of inventions is claimed in one and the same international application, the requirement of unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

PCT Rule 13.2. Applicant asserts that, as amended the currently pending claims meet the requirements set out in PCT Rule 13.2 in that there is at least one "technical relationship" common among those claims. Specifically, the claims comprise the special technical feature of determining *tau* levels as part of a method for the early detection/diagnosis of the types of CNS damage recited in the claims. This "special technical feature" is not disclosed or suggested by

the prior art. Accordingly, Applicant asserts that the currently pending claims now meet the requirements for a finding of "Unity of Invention."

In view of the Amendment to the claims and the arguments presented herein and in accordance with the requirements of PCT Rule 13 and 37 C.F.R. § 1.475, Applicant specifically requests that the instant Restriction Requirement be withdrawn and that all pending claims be examined in the instant application.

Notwithstanding the foregoing request, in accordance with the requirements of 37 C.F.R. §1.143 and in response to the restriction requirement which the Examiner has imposed, Applicant provisionally elects, with traversal, to prosecute claims 1-3 and 5-11, *i.e.*, the Group I claims.

Applicant notes that the Examiner has further requested that Applicant elect species from various "groups," defined by the Examiner. Applicant asserts that the above arguments made concerning the "Unity of Invention" among the pending claims applies *mutatis mutandis* to the various "groups" created by the examiner. Therefore, Applicant contends that Applicant is entitled to examination of all listed "species" in the current application. Nevertheless, in fulfillment of the requirements of 37 C.F.R. §1.143, Applicant provisionally elects the following species in the groups specified by the Examiner (the specified group, the elected species and the claims that read on the elected species are listed as (i)-(vi) as required by the Examiner):

(i) **space-occupying lesions group**: brain metastasis, this species is read on by claims 1-5, 11, and 14-16;

(ii) **invasion or metastasis group**: leukemia, this species is read on by claims 1-4, 6, and 11, and 14-16;

(iii) **organisms group**: viral encephalitis, this species is read on by claims 1-4, 7, 11, and 14-16;

(iv) **anoxia or ischemia group**: stroke, this species is read on by claims 1-4, 8, 11, and 14-16;

(v) **chemical agents group**: chemotherapy, this species is read on by claims 1-4, 9, 11, and 14-16; and

(vi) **physical agent group**: trauma, this species is read on by claims 1-4, 10, 11, and 14-16.

Applicant acknowledges that upon allowance of a generic claim Applicant will be entitled to examination of a reasonable number of "non-elected" species.

The Examiner is invited to contact the undersigned patent agentat (713) 787-1589 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

Matthew L. Madsen
Reg. No. 45,594
Agent for Assignee
INNOGENETICS N.V.

HOWREY SIMON ARNOLD & WHITE, LLP
750 Bering Drive
Houston, Texas 77057-2198
(713) 787-1400

Date: October 4, 2002

CLAIMS:

1. **(Amended)** A method for the early detection and/or quantification of CNS damage in an individual, said CNS damage being caused by ~~[space-occupying lesions]~~ benign primary brain tumors, malignant primary brain tumors, brain metastasis, hydrocephalus, subdural haematoma, and/or parasite derived cysts of the CNS;~~[,]~~ by invasion or metastasis of the CNS;~~[,]~~ by organisms;~~[,]~~ by anoxia or ischemia;~~[,]~~ by chemical agents;~~[,]~~ by physical agents; or by a combination of these mechanisms, said method comprising the step of determining the level of tau in said individual and comparing it to the level of tau in control healthy individuals.

2. **(Amended)** A method for the early in vitro detection and/or quantification of CNS damage in an individual, said CNS damage being caused by ~~[space-occupying lesions]~~ benign primary brain tumors, malignant primary brain tumors, brain metastasis, hydrocephalus, subdural haematoma, and/or parasite derived cysts of the CNS;~~[,]~~ by invasion or metastasis of the CNS;~~[,]~~ by organisms;~~[,]~~ by anoxia or ischemia;~~[,]~~ by chemical agents;~~[,]~~ by physical agents; or by a combination of these mechanisms, said method comprising the steps of:
   - obtaining a sample from said individual,
   - determining the level of tau in said sample and comparing it to the level of tau in control healthy individuals.

3. A method according to claim 2 in which the sample is taken from the cerebrospinal fluid of the individual.

4. A method according to claim 2 in which the sample is taken from the blood derivatives of the individual.

5. **(Twice Amended)** A method according to claims 1 or 2 in which the ~~[space-occupying lesion of the]~~ CNS damage is cause by ~~[is]~~ a benign primary brain tumor, a malignant primary brain tumor ~~[benign or malignant]~~, a brain metastasis, or a subdural haematoma.

6. (Amended) A method according to claims 1 or 2 in which the invasion or metastasis of the CNS is by leukemia, lymphoma or breast cancer.

7. (Amended) A method according to claims 1 or 2 in which the organisms are bacteria or viruses causing encephalitis or meningitis.

8. (Amended) A method according to claims 1 or 2 in which the anoxia or ischemia is caused by stroke, by cerebral infarction, by cerebral hemorrhage, by thrombosis, by perinatal asphyxia, by Binswanger disease or by vasculitis.

9. (Amended) A method according to claims 1 or 2 in which the chemical agent is gene therapy, pharmaceuticals, chemotherapy or exposure to chemical compounds.

10. (Amended) A method according to claims 1 or 2 in which the physical agent is a trauma, stroke, intracranial pressure or radiation.

11. (Amended) A method according to claims 1 or 2 in which CNS damage is detected and/or quantified in order to evaluate the effect of a certain treatment on said CNS damage.

14. **(Amended)** A kit for the early diagnosis of CNS damage in an individual, said CNS damage being caused by ~~[space-occupying lesions]~~ benign primary brain tumors, malignant primary brain tumors, brain metastasis, hydrocephalus, subdural haematoma, and/or parasite derived cysts of the CNS;~~[,]~~ by invasion of the CNS;~~[,]~~ by organisms;~~[,]~~ by anoxia or ischemia;~~[,]~~ by chemical agents;~~[,]~~ by physical agents;~~[,]~~ or by a combination of these mechanisms, comprising a tool for the detection of tau.

15. (Amended) A kit according to claim 16, wherein the marker is tau.

16. (Amended) A kit according to claim 14 characterised in that said kit comprises:

- a monoclonal antibody (primary antibody) which forms an immunological complex with an epitope of tau;
- a secondary antibody
    - which can be a monoclonal antibody recognising an epitope of the tau-primary antibody complex, but not recognising the primary antibody alone, or
    - which can be a polyclonal antibody recognising an epitope of the tau-primary antibody complex but not recognising the primary antibody alone, with said polyclonal antibody being preferably purified by immuno affinity chromatography using immobilized tau or immobilized tau-primary antibody complex;
- a marker either for specific tagging or coupling with said secondary antibody,
- appropriate buffer solutions for carrying out the immunological reaction between the primary antibody and the test sample, between the secondary antibody and the tau-primary antibody complex and/or between the secondary antibody and the marker;
- optionally, for standardisation purposes, a purified protein or a synthetic peptide containing one or more tau epitopes.

17. A method to screen or monitor the effect of compounds which prevent or treat CNS damage comprising the step of determining the level of tau and comparing it to the level of tau in a control sample.